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Award Number: W81XWH-04-C-0083

TITLE: Internet-Based Cervical Cytology Screening Program

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REPORT DATE: April 2005

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;
Distribution Unlimited

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 074-0188

1. AGENCY USE ONLY	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	April 2005	Annual (15 Mar 2004 - 14 Mar 2005)

4. TITLE AND SUBTITLE
Internet-Based Cervical Cytology Screening Program

5. FUNDING NUMBERS
W81XWH-04-C-0083

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8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSORING / MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

12b. DISTRIBUTION CODE

13. ABSTRACT (Maximum 200 Words)

This project explores the combination of computerized automated primary screening of cervical cytology specimens in remote sites with interpretation at remote sites of device-selected images transmitted via the Internet. The project is in 3 phases: 1) hardware/software and interface development and end user training; 2) a 500 case prospective pilot study with hardware/software adjustment, with development of clinically applicable specimen triage and management guidelines; and 3) a 5000 case prospective clinical trial of the completed system, with report and development of training manual.

In the first annual period, phase 1 activities are complete. The hardware/software has been developed and end user training for the phase 2 sites has been accomplished. Institutional Review Board approval has been received at Massachusetts General Hospital (MGH) for all phases and is currently awaiting oversight review, and for phase 1 at Walter Reed (WRAMC) with phase 2 approval expected in April of 2005. Phase 3 IRB applications have been submitted for phase 3 sites (121st Military and US Air Force Academy Hospitals). Phase 2 patient accrual will begin at MGH and WRAMC upon final IRB approval receipt. Installation of equipment at phase 3 sites has begun.

14. SUBJECT TERMS
telecytology, cytopathology, telemedicine, cancer screening, health care information systems

15. NUMBER OF PAGES
53

16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
Unclassified	Unclassified	Unclassified	Unlimited

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Introduction

Cervical cancer is theoretically completely preventable by effective screening using cervical cytology methods (the Pap test). The process of preparing and interpreting Pap tests remains one of the last high-volume manual processes in the clinical laboratory. Recent technological advances in specimen preparation and computerized primary screening make automated approaches to cervical cancer screening possible. In addition, advances in information technology have facilitated the Internet transmission and archival storage of digital images and other clinical information. The combination of automated preparation and screening of cervical cytology specimens, with Internet transmission of selected images, and remote interpretation and reporting of results has not been previously attempted.

This project develops a highly automated cervical cytology screening system, a software interface capable of transmitting and presenting images to remote reading stations, with facility for immediate results reporting back to the specimen source. Clinical studies utilizing this developed system will be performed to test accuracy and functionality against the current on-site manual screening process. Primary development of the system has been accomplished at the Massachusetts General Hospital (MGH) site, and implementation of a pilot study is underway at the MGH and Walter Reed Army Medical Center (WRAMC) sites. Final preparations for the full scale clinical trial are currently being made at the 121st Army and US Air Force Academy Hospitals.

Body

The following is a summation of the work completed to the present time based on the project's accepted Statement of Work. Details follow below in an expanded version of the Statement of Work:

Statement of Work

Task 1: Complete hardware, software and network development required for testing of the internet-based cervical cytology screening system

a) Modify the FocalPoint device to accept, process and analyze ThinPrep specimens - **completed**

b) Adapt FocalPoint hardware for internet transmission of digital images from ThinPrep and SurePath specimens - **completed**

c) Adapt commercial software (Wellogic) to permit rapid and secure transmission of digital images to remote review stations - **completed**

d) Procure and install remote microscopy stations (2) - **completed**

e) Adapt commercial software/hardware (Wellogic) to allow secure, automated reporting of cervical cancer screening results - **completed**

f) Adapt commercial software (Wellogic) to integrate screening results reporting with medical decision support system - **completed pending modification in phase 2**

g) perform initial testing of integrated hardware/software/network - **completed**

Task 2: Develop morphology and terminology for digital images and perform pilot clinical trial

a) Develop a set of learning cases with known diagnostic outcome - **one set completed and second set in development**

b) Develop morphologic criteria for accuracy of interpretation - **ongoing**

c) Develop reporting terminology appropriate for case management - **ongoing**

d) Develop medical decision support algorithms - **ongoing**

e) Perform pilot trial using a set of 500 unknown specimens to identify preliminary system performance characteristics – **awaiting IRB approval (pilot trial IRB approval received - MGH, pending approval – WRAMC, both will require USAMRMC oversight approval – MGH protocol submitted and pending))**

f) Modify procedures/equipment based on pilot trial results - **future**

g) Develop training methods/materials for clinical practice - **future**

Task 3: Complete large, prospective clinical trial of the performance of the internet-based system compared to conventional on-site screening.

a) Develop and receive approval for clinical trial protocol and consent forms - **protocols developed and IRB submissions completed - pending review**

b) Install equipment at selected sites - **ongoing**

c) Train clinical personnel participating at selected sites - **future**

d) Conduct the clinical trial - **future**

e) Perform trial data analysis - **future**

f) Prepare report of trial with implementation recommendation - **future**

Expanded discussion of the Statement of Work

Prior to initiation of the project, Dr. David Wilbur (MGH principal investigator), Dr. John Eichhorn (MGH co-investigator), and Doug McClure and Kimberly Lacey (project managers in Partners Telemedicine Group) made a site visit to WRAMC in order to brief army investigators led by Dr. Barbara Crothers (Army principal investigator) on the background and concept of the project and to plan initial implementation. Dr. Wilbur also went on a site visit (as part of an already preplanned trip) to the 121st Military Hospital in Seoul, Korea and briefed Dr. Min Ro (site principal investigator) and his staff on the project and to assess space and other needs at this site. A similar site visit is currently being planned prior to phase 3 initiation at the USAFA clinical site with Dr. Emily Miller (site principal investigator).

The first manuscript related to the project was accepted for publication in Cancer Cytopathology during this report period. This manuscript details the project concept and the initial feasibility study that was performed by MGH investigators prior to and in support of the current research award. Ongoing efforts and rationale for the current project are detailed in the manuscript. (see appendix for copy of accepted manuscript)

Task 1: Complete hardware, software and network development required for testing of the internet-based cervical cytology screening system

a) Modify the FocalPoint device to accept, process and analyze ThinPrep specimens - **completed**

The FocalPoint System has been previously approved for use with conventionally prepared and SurePath (a TriPath proprietary method) cervical cytology slides. Engineers at TriPath developed the changes necessary to accommodate ThinPrep slides by changing the overall scan area, and made adaptations in the software that affected scoring of the slide for probability of

abnormality being present, the identification of individual potentially abnormal cells, and to assess the adequacy of the specimen.

b) Adapt FocalPoint hardware for internet transmission of digital images from ThinPrep and SurePath specimens - **completed**

Working with Wellogic software engineers, TriPath engineers developed a method by which field of view images collected for each of the scanned slides could be queried automatically from the FocalPoint database. These images, along with other slide data, such as case identifiers, slide score quintile (proportional to probability of abnormality being present) and adequacy information, could be automatically downloaded into the reading/reporting software.

c) Adapt commercial software (Wellogic) to permit rapid and secure transmission of digital images to remote review stations - **completed**

Wellogic engineers developed this functionality based on an "off the shelf," HIPAA compliant platform ("Consult") already utilized in other secure medical consultation applications.

d) Procure and install remote microscopy stations (2) - **completed**

After an evaluation of current commercially available telepathology systems (Nikon, Olympus, and TriPath products were evaluated), the Trestle System was found to be the most applicable to the current second tier review

task. Two such systems were acquired and installed - one at Massachusetts General Hospital, the other at the US Air Force Academy Laboratory. The 121st Military Hospital Laboratory already has a Trestle System in place for Army telepathology applications - this system, already in place, can be adapted for use in the project.

e) Adapt commercial software/hardware (Wellogic) to allow secure, automated reporting of cervical cancer screening results - **completed**

Wellogic engineers developed this software package as noted above. See appendix for appearance of the software interface with fields for data entry, cytotechnologist, and cytopathologist evaluation.

f) Adapt commercial software (Wellogic) to integrate screening results reporting with medical decision support system - **completed pending modification in phase 2**

Wellogic engineers developed this software package as noted above. Following phase 2 testing further modifications will be made based on functionality assessments.

g) perform initial testing of integrated hardware/software/network - **completed**

The integrated hardware/software/network package received initial testing of functionality by MGH investigators using the initial set of 25 SurePath and ThinPrep slides scanned on the FocalPoint System and

output information downloaded into the Wellogic program.

Task 2: Develop morphology and terminology for digital images and perform pilot clinical trial

a) Develop a set of learning cases with known diagnostic outcome - **one set completed and second set in development**

An initial set of 25 slides of known diagnosis was developed for initial system functionality testing. A 100 slide test set of ThinPrep slides with known diagnosis has been entered into System database for training and diagnosis/ terminology /management algorithm development. A second set of 100 SurePath slide cases is being collected at the time of this report. WRAMC personnel had prior ThinPrep morphology training, but required training in SurePath morphology interpretation. This training, with proficiency testing and certification, was accomplished on site at WRAMC, and was performed by MGH personnel. MGH personnel had training and certification in both ThinPrep and SurePath morphology interpretation prior to the initiation of this project.

b) Develop morphologic criteria for accuracy of interpretation - **ongoing**

At the initiation of the project, the investigators plan to capture all possible information on each case – meaning making both general and specific interpretations on each case (according to the 2001 Bethesda System terminology

for cervical cytology) and recording all morphologic clues used in case interpretation. Data analysis will guide the level of precision of interpretation that will be utilized in the clinical trial. An example of the data collection material for each case in this phase is illustrated in the appendix.

c) Develop reporting terminology appropriate for case management - **ongoing**

At the initiation of the project, the investigators plan to capture all possible information on each case – meaning making both general and specific interpretations on each case and recording all morphologic clues used in case interpretation. Data analysis from the initial and phase 2 studies will guide the level of precision of interpretation that will be utilized in the clinical trial.

d) Develop medical decision support algorithms - **ongoing**

Will depend on outcome of phase 2 pilot study.

e) Perform pilot trial using a set of 500 unknown specimens to identify preliminary system performance characteristics - **awaiting IRB approval (pilot trial IRB approval received - MGH, pending approval – WRAMC, both will require USAMRMC oversight approval – MGH protocol submitted and pending)**

MGH and WRAMC consented patients will be enrolled following phase 2 IRB and oversight approvals.

f) Modify procedures/equipment based on pilot trial results - **future**

g) Develop training methods/materials for clinical practice - **future**

Task 3: Complete large, prospective clinical trial of the performance of the internet-based system compared to conventional on-site screening.

a) Develop and receive approval for clinical trial protocol and consent forms - **protocols developed and IRB submissions completed - pending review**

b) Install equipment at selected sites - **ongoing**

Equipment has been installed to date as follows:

1) MGH - 3 high resolution monitors installed for reading stations, one personal computer with high resolution monitor, a Trestle telepathology system.

2) WRAMC – 2 high resolution monitors installed for reading stations.

3) USAFA – a Trestle telepathology system.

Equipment slated to be installed in the future:

1) 121st Military Hosp – FocalPoint Primary Screening System

2) USAFA – FocalPoint Primary Screening System

3) Information technologies issues at the DOD clinical trial sites are being addressed and progress toward installation is being made.

c) Train clinical personnel participating at selected clinical sites - **future**

d) Conduct the clinical trial - **future**

e) Perform trial data analysis - **future**

f) Prepare report of trial with implementation recommendation – **future**

Key Research Accomplishments

1) Modification of FocalPoint System to accommodate ThinPrep Slides

2) Development of Wellogic database, reading station, and report generation software package

3) Interfacing of the FocalPoint and Wellogic systems

4) IRB submissions

Phase 1 at MGH and WRAMC approved

Phases 2 and 3 at MGH approved by local IRB, USAMRMC review pending

Phase 2 at WRAMC submitted, local IRB approval anticipated April 2005

Phase 3 at 121st and USAFA submitted

5) Learning test slide set development in progress

6) Development of morphology criteria, terminology, and clinical algorithms is ongoing

7) Pilot test consented patient accrual at MGH and WRAMC anticipated in May 2005

8) Equipment installation at MGH and WRAMC sites completed

9) Equipment installation at clinical sites in progress

10) DODinformation technology integration processes are in progress. The AMEDD 25-1 process has been initiated through the Walter Reed DOIM Cange Control Board (CCB) and phase I of the DOD Information Technology Security Certification and Accreditation Process (DITSCAP) process is nearly complete. The SSAA (System Security Authorization Agreement) is initiated. Completed documents include the mni-Business Case Analysis (BCA), the initial Networthiness preview, initial DITSCAP

preview and Schedule T. A functional thrust owner (FTO) at MEDCOM has been assigned to the project.

Reportable Outcomes

1) First publication accepted in Cancer Cytopathology - see appendix

Conclusions

1) System development is progressing satisfactorily.

2) IRB and DOD information technology issues are being addressed.

3) Morphology training sets have been (and continue to be) developed.

4) System testing with consented patient cases is slated to begin within the next month after this report.

5) System installation at clinical sites is progressing according to plan and stated timeline.

Appendix

1) Cancer Cytopathology accepted feasibility study manuscript

2) Example of case data capture form which will be utilized for interpretation and criteria development

3) Wellogic software computer review/reporting station screens

4) Copies of MGH IRB-approved consent form and patient information brochure (pilot trial - phase 2)

A NOVEL AUTOMATED SCREENING AND INTERPRETATION PROCESS FOR CERVICAL CYTOLOGY USING INTERNET TRANSMISSION OF LOW RESOLUTION IMAGES: A FEASIBILITY STUDY

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Presented in part at an annual meeting of the United States and Canadian Academy of Pathology, Washington, D.C., March 22-28, 2003.

Acknowledgments: The preliminary work was supported in part by the Edmund C. Lynch, Jr., Cancer Fund. The ongoing portions of this project are supported by the U.S. Army Medical Research and Materiel Command under Contract No. W81XWH-04-C-0083.

Disclosure: Dr. Wilbur is a member of the speakers' bureau of TriPath Imaging, Inc.

Concise Abstract:

A system of remote cervical cytology image interpretation using an automated screening device and internet transmission is tested. Preliminary results show that accuracy may be acceptable and that the procedure may provide a method of centralized specimen interpretation or triage or both.

Running title:

Internet cervical screening

Pages: 22 (text, 19; tables, 3)

Figures: 6

ABSTRACT

Background: Transmission over the internet of low-resolution images acquired by automated screening of cervical cytology specimens has the potential to provide remote interpretation, and hence centralization of a cytology workforce.

Methods: Liquid-based cervical cytology specimens were scanned using the FocalPoint® System (TriPath). Ten black-and-white images having the highest probability of containing abnormality were acquired from each of 32 reference cases (16 - negative; 3 - atypical squamous cells of uncertain significance (ASC-US); 5 - low-grade squamous intraepithelial lesions (LSIL); 5 - high-grade squamous intraepithelial lesions (HSIL); 1 - adenocarcinoma in situ; 2 - carcinoma) and transmitted as e-mail attachments in JPEG format to remote reading stations. The cases were interpreted independently by two pathologists and assigned to either of two groups: 1) suspicious for ≥HSIL; or 2) ≤LSIL. The interpretations were compared to the reference diagnoses. The cases were then randomized and the image sets redistributed to the pathologists for another round of interpretation and scoring.

Results: The initial and subsequent trials yielded similar results. Pooling the interpretations of the two pathologists, the concordance rate between reference and assigned diagnostic groups for each of the two trials was 84%, the false positive rate 8.3% and the false negative rate 37.5%. Review of the discrepant cases revealed subtle cellular changes that might be utilized to reduce errors, and with training, optimize sensitivity and specificity.

Conclusion: This procedure shows promise for allowing remote interpretation of device-selected images. This procedure may represent an effective way to centralize cervical cytology services and to allow the provision of services to previously unscreened populations lacking effective cytology infrastructure.

Key Words: Cervical cytology, automation, internet, telepathology, telecytology, FocalPoint

INTRODUCTION

The FocalPoint® screening system for cervical cytology (TriPath Imaging, Inc., Burlington, NC) is approved by the United States Food and Drug Administration (FDA) for use in the primary screening of conventional and SurePath® (TriPath) liquid-based slides. Studies have shown that this automated system efficiently and reliably identifies more abnormal cases than does manual screening alone and that it can be used in the triage of slides to "no manual review" or "complete manual review" (1-3). Inherent to the operation of the FocalPoint® device is its ability to identify fields of view (FOV) on each slide that contain individual cells or cell groupings that have the highest probability of being abnormal (Figure 1) (4). In doing so, the device captures low resolution JPEG images designed to allow accurate localization to observers during subsequent manual microscopic review. This image capture capability also makes possible the rapid transmission of such images over the internet for interpretation at remote sites. Although digital transmission and interpretation of cytology images has been investigated by others (5-7), the combination of automated screening and internet-based telecytology remote interpretation has not been explored. Because it bypasses on-site manual review and the large-scale transportation of perishable glass slides, such a system could lead to substantial centralization and optimization of cytology screening resources. The use of these complimentary technologies could also allow the introduction of cervical cancer screening programs to countries where none currently exist.

In order to implement such a program, it will be necessary to show that accurate and reliable interpretations can be made using FOV review alone on a computer monitor,

without the benefit of a full manual microscopy screening. Microscopic FOV review with triage to full manual screening when abnormality is initially identified has been shown to be potentially very accurate (4); however, the operating characteristics of the review of only low resolution images, by its very nature, might show a lower sensitivity for the detection of disease. In addition, lack of the benefit of full screen or "through the microscope" review might be expected to provide less information on specimen adequacy, reactive changes, organisms, and subtle low-level abnormalities such as atypical squamous cells. For an intended application of high-grade specimen triage, however, it may be sufficient to identify those lesions requiring prompt intervention. The present study uses this approach with a triage point at the "suspicious for $\geq$HSIL" cut-off level to assess the feasibility of remote interpretation of digital images obtained via automated screening and transmitted over the Internet.

MATERIALS AND METHODS

The study population consisted of a set of 32 reference SurePath® liquid-based cervical cytology slides from the files of the Massachusetts General Hospital with known diagnoses confirmed by one of the study pathologists (DCW) approximately 2 months prior to the study initiation. The interpretations were made using the criteria of the 2001 Bethesda system (8). The set included cases of carcinoma (two), adenocarcinoma in situ (AIS) (one), high-grade squamous intraepithelial lesion (HSIL) (five), low-grade squamous intraepithelial lesion (LSIL) (five), atypical squamous cells of undetermined significance (ASC-US) (three), and negative for intraepithelial lesion or malignancy (NILM) (sixteen). The HSIL, AIS, and cancer cases were biopsy confirmed. Of the NILM cases, four showed Candida species or Trichomonas vaginalis organisms, two were atrophic, and one showed bacterial vaginosis (Table 1).

All patient identifier information was delinked from the cases and the slides were scanned at a remote site (TriPath, Redmond, WA) on the FocalPoint® GS System and a set of the ten highest scoring field of view (FOV) images were captured in the JPEG compressed format (image size, 12-16KB each). The FocalPoint® GS System captures only black and white images and each image corresponds closely to a microscopic 200x magnification when viewed on a monitor. Sets of ten JPEG images per slide were bundled as e-mail attachments and transmitted via the Internet to reading stations at the Massachusetts General Hospital. Each "reading station" was a Partners network computer (Microsoft Windows 2000 Professional) and the images were opened using Microsoft Outlook 2000 and Internet Explorer software, and reviewed on standard 17-

inch desktop monitors. An example of an e-mail received at a review site is shown in Figure 2.

Each of the 32 study cases was interpreted independently by two board-certified cytopathologists with a combined 30 years of postgraduate experience (JHE, DCW) who were masked to the reference diagnoses. During the review, notations were made for learning purposes as to why a given diagnosis was favored. Cases were diagnosed as specifically as possible and were then assigned in a binary triage process to either of two categories: 1. NILM or "low-grade" (normal findings; reactive changes; ASC-US; LSIL); 2. Suspicious for an HSIL or more serious process (atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion (ASC-H); HSIL; cancer; or cases suspicious for any of these diagnoses). A binary classification was utilized because a goal of the study was to determine whether the combination of automated screening and remote transmission of low-resolution images could be utilized to triage patients with a cutpoint of biological significance for true precancerous high-grade lesions versus negative cases and those with low-grade or possibly transient human papillomavirus (HPV) infections. After both pathologists had recorded their categorizations of each case, the "test" interpretations were compared to the reference diagnoses. With the knowledge of this comparison between "test" and "reference" categorizations, each of the pathologists had an opportunity to view again the bundled digital images for any given case, or review any notations that they had recorded at the time of the initial interpretation. Glass slides were not studied together with the black-and white images. After a two-month hiatus, the 32 cases then were "shuffled" (randomized) and their bundled images retransmitted to the two reviewers for a second round of interpretations

to assess whether their ability to categorize the lesions was improved by their knowledge of the types of errors that had been made (or their threshold bias) in the first round. The results of the first and second trials were compared for each of the two pathologists. From the pooled interpretations of the two pathologists, rates of concordance ((true positive + true negative)/total), false positivity (false positive/total negative), false negativity (false negative/total positive), sensitivity (true positive/(true positive + false negative)), and specificity (true negative/(true negative + false positive)) were calculated for both trials, and compared.

RESULTS

Figures 3-6 show representative FOV images from selected cases that were interpreted as NILM, LSIL, HSIL and carcinoma, respectively.

Compared with standard light microscopy, the images displayed on the computer monitor showed poorer resolution for a given degree of magnification and their plane of focus could not be manipulated. These characteristics resulted in poorer definition of the chromatin texture in small nuclei, and the possible lack of detection or appreciation of objects of very small dimensions such as some microorganisms. From the standpoint of the binary categorization used in the present study, these limitations were most problematic when considering the distinction between benign squamous metaplasia and the cells of HSIL (most notably those of moderate squamous dysplasia), particularly when just a few single cells were available in the FOVs for review. Low image resolution and the lack of a full color spectrum also made the evaluation of subtle

cytoplasmic qualities more challenging, particularly in the smaller cells of a given population.

The most useful clues in the identification of dysplasia and its categorization as low-grade or high-grade were found to be nucleus-to-cytoplasm ratio, nuclear shape, the degree of hyperchromasia, the presence or absence of HPV-associated cytopathic perinuclear halos, and the evaluation of aggregates of potentially abnormal cells for their cellular relationships (three-dimensionality, cellular distribution and overlap, orientation, and the degree of variation in size and shape). These features were not affected (or only to a limited degree) by the decreased resolution, fixed plane of focus and loss of color. In addition, an increased emphasis on background features (brisk inflammation or tumor diathesis) could be used in some cases to compensate for the loss of fine detail. Each pathologist spent lessn than 5 minutes per case on average to review the images and render an interpretation. No attempt was made to formally time study this feature in the study.

The reference diagnostic groups and those assigned by each of the two pathologists in the initial and subsequent trials are compared in Table 2. Both pathologists had rates of concordance between test and reference categories exceeding 81% in each of the two trials. One pathologist tended to under diagnose cases suspicious for high-grade lesions in the first trial, with improved sensitivity in the second trial. The other pathologist tended to over diagnose cases suspicious for high-grade lesions in the first trial, and showed improved specificity in the second trial.

Table 3 combines the results of the two pathologists in each of the two trials, respectively, and compares the reference diagnostic groups to the interpretations of the

pathologists. From the latter tabulation, the concordance rate between the test and reference interpretations was 54/64 = 84 %, the false positive rate 4/48 = 8.3 % and the false negative rate 6/16 = 37.5 %, for both trials. The rates of sensitivity and specificity were 63% and 92%, respectively, for both trials.

DISCUSSION

Worldwide, it has been estimated that 471,000 women per year are diagnosed with cervical cancer, and 233,400 women per year die from the disease (9). Overall, cervical cancer remains a leading cause of death of young women in countries that lack any screening program (10). On the other hand, the incidence and mortality figures have decreased substantially in countries where population-based screening programs have been instituted (11). In the United States, for instance, it has been estimated that the incidence of cervical cancer has decreased by 50 percent in 50 years (12) and that the mortality has decreased by 70 percent since widespread screening was instituted in the 1950's (13). The incidence and mortality rates for cervical cancer in the United States were recently reported to be 13,000 and 4,000 women per year, respectively (14), but, again, a majority of these deaths occur among women in sub-populations that are largely under-screened (15). Women in many developed countries benefit not only from periodic sampling of cells from the cervix and an adequate pool of trained specialists (cytotechnologists and cytopathologists) to screen and interpret these specimens, but also from new technologies such as liquid-based specimen preparations and computerized automated screening. From the perspective of healthcare delivery systems in regions of the world that lack any cytology infrastructure, however, the most difficult and costly hurdle to the implementation of screening is the establishment of a trained cytology workforce. Even in the United States, deficiencies in this workforce are anticipated (16), particularly in certain settings such as the military health care system.

It is the hypothesis of the present study that internet transmission of images derived from automated screening devices for interpretation at remote locations has the

potential to provide an effective screening program for countries lacking a trained cytology infrastructure, and to provide a more efficient, economical, and centralized way of triaging patient samples.

The results of this pilot study provide preliminary feasibility support for this hypothesis. The system of image selection, digital storage, electronic transmission and remote interpretation worked effectively. Diagnoses were rendered on small, finite sets of images that had been selected and encoded by an automated screening device, sent via the Internet from a remote location, and interpreted at a centralized site. After independent masked reviews by two pathologists in two separate testing events,case discrimination at the "suspicious for HSIL or a more serious lesion" level of triage showed a false negative rate 37.5%, a false positive rate of 8.3%, and an overall concordance rate of 84%, for each of two trials. Stated differently, the specificity was 92% and the sensitivity was 63%. Although the relatively high false negative rate compares unfavorably to the current standard of less than 10% for HSIL+, the authors observed that experience and learning obtained between the first and second phases of this relatively small trial had the potential to improve the sensitivity in ongoing use. In addition, if the desired goal is the identification of as many patients with high-grade lesions as possible in populations with limited screening, this process offers an advantage over no screening at all. Ultimately, the sensitivity of the screening process might be augmented when coupled with developing molecular assays, such as those for HPV-associated antigens and proliferation markers, which could also be performed and interpreted remotely over the same web-based network (17).

The present data do suggest, however, that interpretative accuracy with this system can be improved through a re-assessment of the diagnostic criteria and training in the use of them. It may be conjectured that the interpretative criteria that are most useful in this new modality are different from those that one is accustomed to relying upon in manual microscopy. Image magnification could not be increased and lack of fine focusing imposed limits on the visualization of fine chromatin detail and group morphology. In this context, a more subtle assessment of background material and cell-cell relationships received greater emphasis. Both pathologists altered their performance in the second trial after a review of their mistakes in the first, but they did so in opposite measures: "pathologist 1" improved his specificity from the first trial to the second, while "pathologist 2" improved his sensitivity.. Moreover, the utilization of alternative triage cutoff points not only might alter the sensitivity and specificity rates, but also could be tailored to different public health care objectives.

The system we describe differs from manual microscopic screening in at least five respects that may decrease its comparative performance: 1) a finite set of images (FOVs) is selected by the automated screening device; 2) the image resolution is lower than that of microscopy; 3) the plane of focus is fixed; 4) the magnification is pre-determined; and, 5) the images are black-and-white. A factor to be analyzed in future studies is the optimum number of FOVs that need to be examined. Will increasing the number of FOVs presented improve the accuracy? The size and resolution of the presented FOVs also can be altered. Will changing of these parameters improve the accuracy? Finally, the ability to image in color and the creation of scanned "virtual" FOVs with the ability to focus through planes need to be investigated as means of improving the overall accuracy

without compromising the novel issues of internet transmission, remote interpretation and centralization capability.

This pilot study has obvious limitations. The study population was a small teaching set with known diagnoses, which is not equivalent to a population of patients examined prospectively. Only specimens prepared using the SurePath® method were studied, primarily because the FocalPoint® screening equipment is calibrated and FDA-approved only for their use; accordingly, the results obtained from conventionally smeared or ThinPrep® liquid-based slides (Cytyc, Boxborough, MA) might differ. Finally, the pathologists by necessity were modifying their habitual criteria as the study progressed. Although their performance improved after a review of their mistakes in the first trial, it is not known if this was due to a modification of their criteria or diagnostic thresholds, subconscious (or conscious) compensation for their biases in the initial test, or memory of individual difficult cases or images. Future planned prospective trials will address these issues.

The screening system presented was conceived as a potential solution to a need for population-based cervical cancer screening in the many countries of the world that currently lack a cytology-screening infrastructure. Such a system would serve an immediate need in developing countries that have a large "at-risk" population of unscreened women, a commitment to improving public health, some medical care capabilities and some telecommunications infrastructure, but an absence or limited supply of a trained cytology workforce. Potentially, the number of women residing in such countries greatly exceeds that of the developed countries with active screening programs in place. The images utilized in the present study required very modest

amounts of memory (<20KB), and therefore would not require significant bandwidth for transmission. At comparatively low cost, automated screening devices could be located in these regions, and personnel trained only in their operation and maintenance and in the preparation of liquid-based specimens could tend them. Images derived from such specimens then would be transmitted and interpreted elsewhere, and the diagnoses, triage groups or both returned electronically to a party responsible for the care of the patient.

Another potential application would be for far-flung organizational systems such as the military cytology service. Such services strive to apply United States "standard of care" for military personnel throughout the world, often with a highly mobile and difficult-to-track group of patients and caregivers. A cruder triage of cases into diagnostic groups that do or do not require timely medical intervention, however, may suffice for many of the costly deployment decisions that could arise. Automated screening equipment could be located at existing military medical facilities, sites that nevertheless are too remote for a fixed pool of trained cytotechnologists. The necessity of making rapid deployment decisions and the declining availability of cytology human resources could be used to argue for the use of such a system with a centralized interpretive service and a linked electronic reporting system that would automatically follow the patient and health care provider to any point on the globe.

In conclusion, the aforementioned scheme represents a novel melding of two complementary technologies - the Internet and computerized automated screening. This pilot study demonstrated the feasibility of this methodology with the possibility of improvements from further training and refinement of hardware, incorporation of ancillary markers, and investigation of clinically relevant endpoints. At its present level

of performance it appears to offer an advantage over no screening for geographic areas that lack a cytology infrastructure. A much larger and well-designed clinical trial is required, however, before its application to problems public health can be considered. Finally, it has the potential to greatly enhance efficiency and centralization of cytology services for organizations maintaining large and complex cytology infrastructures such as the United States military services, or large laboratory organizations.

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17. References from ASC meeting on molecular markers

Table 1. Diagnoses of Reference 32 Cases.

Diagnosis	Number of cases
Carcinoma	2
Squamous	1
NOS	1
AIS	1
HSIL	5
LSIL	5
ASC-US	3
NILM	16
Candida species	3
Atrophy	2
Trichomonas vaginalis	1
Bacterial vaginosis	1
NOS	9

KEY: NOS, not otherwise specified; AIS, adenocarcinoma in situ; HSIL, high-grade intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion; ASC-US, atypical squamous cells of undetermined significance; NILM, negative for intraepithelial lesion or malignancy.

Table 2. Comparison of Test and Reference Diagnostic Groups; First and Second Trials of Each Pathologist. *

	Reference diagnostic category:	
	NEG, ASCUS, LSIL	≥ HSIL
Pathologist 1 Interpretation:		
Negative or LSIL	24 (22)	6 (2)
At least suspicious For HSIL	0 (2)	2 (6)
Pathologist 2 Interpretation:		
Negative or LSIL	20 (22)	0 (4)
At least suspicious for HSIL	4 (2)	8 (4)

*Expressed as number of cases in the initial (subsequent) reviews.

KEY: NEG, negative for dysplastic atypia; ASC-US, atypical squamous cells of uncertain significance; LSIL, low-grade squamous intraepithelial lesion; HSIL, high-grade squamous intraepithelial lesion.

Table 3. Comparison of Test and Reference Diagnostic Groups; Composite Results of Both Pathologists.

	Reference diagnostic category:	
	NEG, ASC-US, LSIL	≥ HSIL
Assigned diagnostic category, both pathologists:		
Negative or LSIL	44 (44)	6 (6)
At least suspicious for HSIL	4 (4)	10 (10)

*Expressed as number of cases in the initial (subsequent) reviews.

KEY: NEG, negative for dysplastic atypia; ASC-US, atypical squamous cells of uncertain significance; LSIL, low-grade squamous intraepithelial lesion; HSIL, high-grade squamous intraepithelial lesion.

FIGURE LEGEND

Figure 1. FocalPoint® GS reviewing station, showing black and white image of the field of view captured in the lower left part of the instrument (box).

Figure 2. Example of an e-mail received at a review site, with ten image icons.

Figure 3. Negative case field of view images.

Figure 4. LSIL case field of view images; aggregate of cells with large irregularly-shaped hyperchromatic nuclei and perinuclear halos.

Figure 5. HSIL case field of view images; individual small cells with increased nucleus-to-cytoplasm ratio and irregular hyperchromatic nuclei.

Figure 6. Carcinoma case field of view images; a tumor diathesis is a useful clue.

Case Data Collection Sheet – Interpretation and Criteria

1) Case number

2) General interpretation NILM Abnormal

3) Specific interpretation NILM ASC-US AGC

LSIL HSIL Cancer

Comments or other interpretation

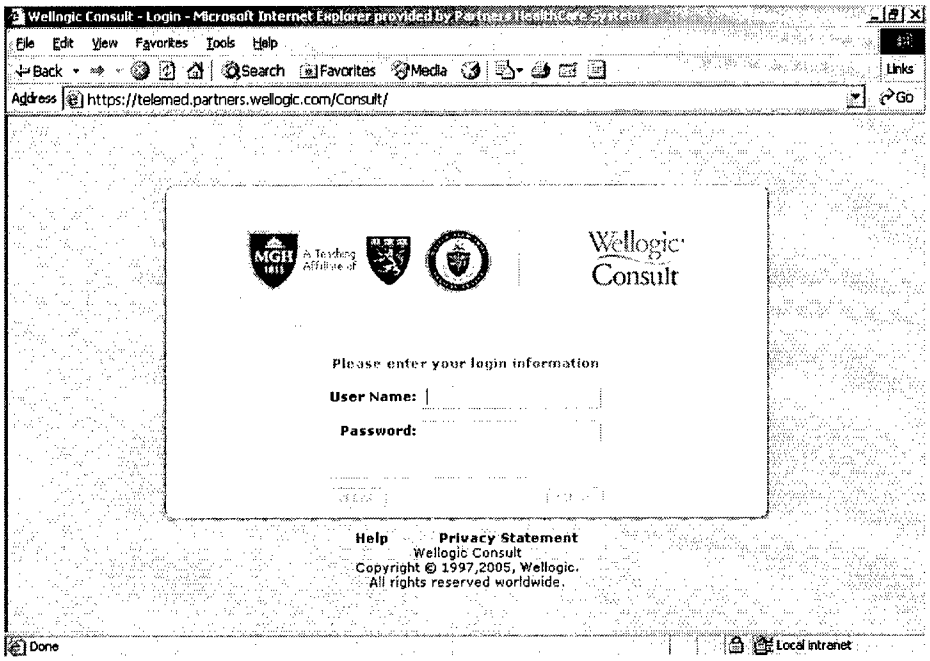
4) Images with abnormality

#first noted with abnormal finding and the abnormality noted

Note all fields with abnormal findings and the abnormality noted

5) Any comments about the case – tips/observations

6) Reference diagnosis and discussion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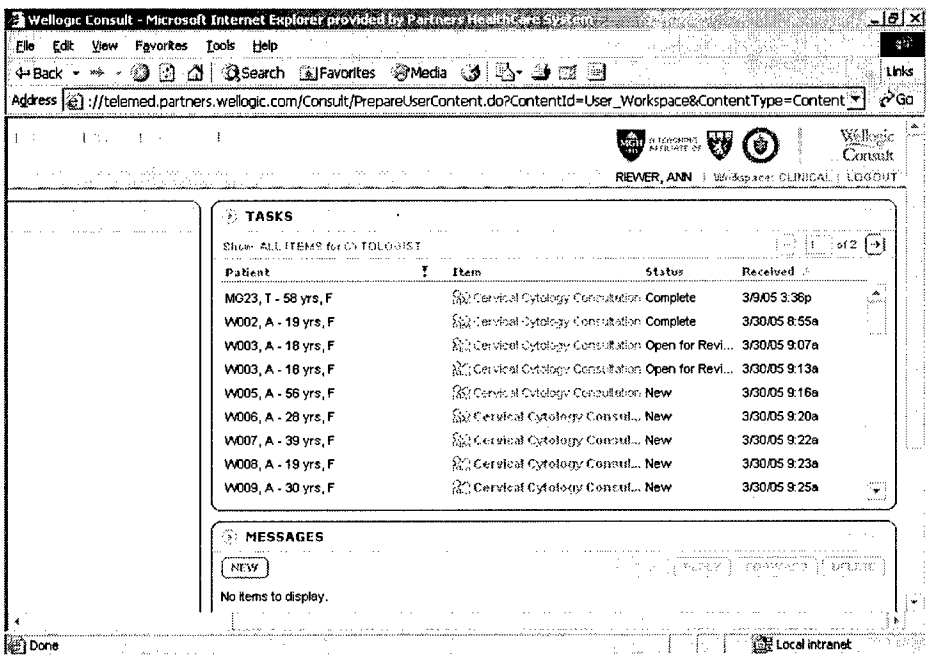
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MG23, T - 58 yrs, F Cervical Cytology Consultation Complete 3/9/05 3:36p
W002, A - 19 yrs, F Cervical Cytology Consultation Complete 3/30/05 8:55a
W003, A - 18 yrs, F Cervical Cytology Consultation Open for Revi... 3/30/05 9:07a
W003, A - 18 yrs, F Cervical Cytology Consultation Open for Revi... 3/30/05 9:13a
W005, A - 56 yrs, F Cervical Cytology Consultation New 3/30/05 9:16a
W006, A - 28 yrs, F Cervical Cytology Consul... New 3/30/05 9:20a
W007, A - 39 yrs, F Cervical Cytology Consul... New 3/30/05 9:22a
W008, A - 19 yrs, F Cervical Cytology Consul... New 3/30/05 9:23a
W009, A - 30 yrs, F Cervical Cytology Consul... New 3/30/05 9:25a
MESSAGES
NEW
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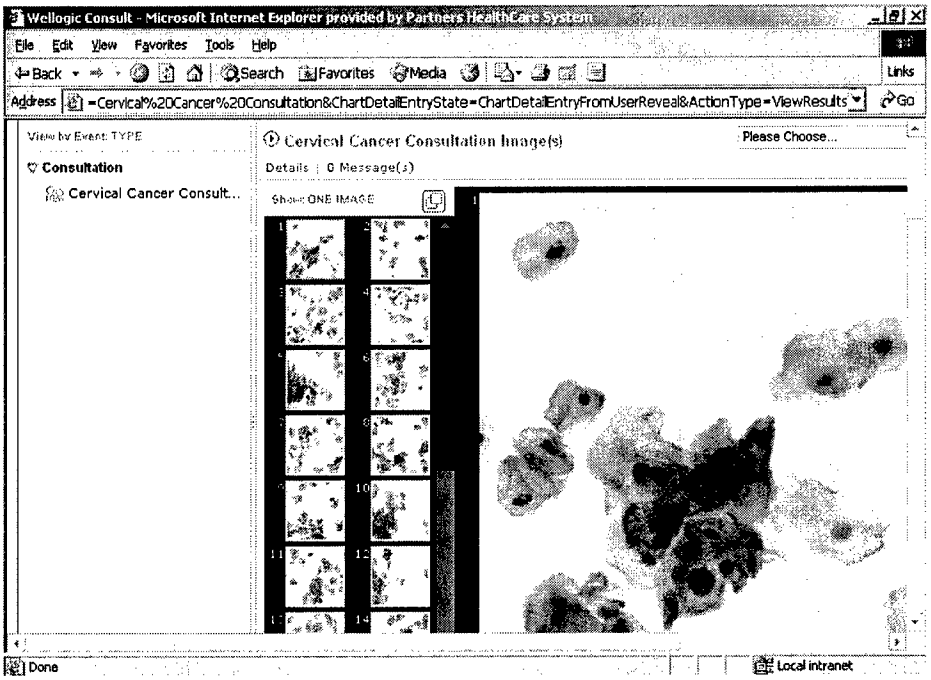
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Research Consent Form

Brigham and Women's Hospital
Massachusetts General Hospital
Newton-Wellesley Hospital
North Shore Medical Center
Spaulding Rehabilitation Hospital
Faulkner Hospital
Partners Community HealthCare, Inc.
Version 5.1.1 - November 2004

Subject Identification

Protocol Title: Internet-Based Cervical Cytology Screening Program

Principal Investigator: David C. Wilbur, M.D.

Site Principal Investigator: David C. Wilbur, M.D.

Description of Subject Population: Women above the age of 18 years having Pap tests performed

PURPOSE

We would like permission to enroll you as a participant in a research study. The purpose of the study is to determine if the Pap test can be accurately performed using images selected by a computer and transmitted to a remote location via the internet. The study will enroll approximately 250 patients from the Massachusetts General Hospital site and approximately 5000 patients overall.

STUDY CONTACTS

David C. Wilbur, M.D., Dept. of Pathology, Massachusetts General Hospital
55 Fruit Street, Warren 120
Boston, MA 02114
617-726-7943

PROCEDURES

During your visit, a Pap test is being taken for your routine gynecologic care. Following routine completion of this test in the clinical laboratory, your slide would be entered into the study. At that time it will be screened by a computer and images selected for transmission to a remote interpretation station. The images will be interpreted by study personnel and the result compared to the clinical result already obtained from your routine care. No genetic testing will be performed.

COSTS

There is no cost to you if you enroll in this study. You or your medical insurer will be charged as usual for routine care, including your Pap smear.

RISKS AND DISCOMFORTS

There are no risks to you in this study as no additional samples will be used beyond those already obtained in the course of your routine care.

Subject Population:	Women above the age of 18 years having Pap tests performed		
IRB Protocol Number:	2003P-001658	Sponsor Protocol Number:	n/a
Consent Form Valid Date:	March 10, 2005	Amendment Number Approved:	1
IRB Expiration Date:	August 26, 2005	Amendment Approval Date:	March 1, 2005

Research Consent Form

Subject Identification

BENEFITS

This study may benefit you directly if it detects an abnormality that was not identified on your routine clinical test. This is anticipated to be a very rare circumstance.
The program could provide future benefit to patients as it could allow Pap tests to be performed on patients in remote areas where the service is not currently available.

ALTERNATIVES

The alternative is to not choose to participate.

By consenting to participate, you authorize the use of your Pap test specimen to be used in the research described above.

If this study is successful and a product or service is developed and sold, there are no plans to provide financial compensation to you.

The Partners Health System could benefit financially from the commercial development of this system. The investigators do not have any personal financial interest in the study outcome.

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Subject Identification

PRIVACY AND CONFIDENTIALITY

Federal law requires Partners HealthCare System, Inc. and its affiliated hospitals, researchers, health care providers, and physician network to protect the privacy of information that identifies you and relates to your past, present, and future physical and mental health and conditions ("protected health information"). If you enroll in the research described in this consent form, your "protected health information" will be used and shared with others as explained below.

1. **What protected health information about me will be used or shared with others during this research?**
   - ☒ Existing medical records.
   - ☐ New health information created from study-related tests, procedures, visits, and/or questionnaires.

2. **Why will protected health information about me be used or shared with others?**
   - The main reasons include:
     - to conduct and oversee the research described earlier in this form;
     - to ensure the research meets legal, institutional, and accreditation requirements; and
     - to conduct public health activities (including reporting of adverse events or situations where you or others may be at risk of harm).
   - Other reasons may include for treatment, payment, or health care operations. For example, some medical information produced by this study may become part of your hospital medical record because the information may be necessary for your medical care. (You will also be given the Partners' Notice for Use and Sharing of Protected Health Information which provides more information about how Partners and its affiliates use and share protected health information.)

3. **Who will use or share protected health information about me?**
   - Partners and its affiliated researchers and entities participating in the research will use and share your protected health information. In addition, the Partners review board that oversees the research at Partners and its affiliated staff who have a need to access this information to carry out their responsibilities (for example, oversight, quality improvement, and billing) will be able to use and share your protected health information.

4. **With whom outside of Partners Healthcare System may my protected health information be shared?**
   All reasonable efforts will be made to protect the confidentiality of your protected health information, which may be shared with the following others for the reasons noted above:
   - Outside individuals or entities that have a need to access this information to perform functions on behalf of Partners and its affiliates (for example, data storage companies, insurers, or legal advisors).
   - ☒ The sponsor(s) of the study, its subcontractors, and its agents: Department of Defense
   - ☐ Other researchers and medical centers participating in this research, if applicable.

Subject Population:	Women above the age of 18 years having Pap tests performed		
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- ☒ Federal and state agencies (for example, the Department of Health and Human Services, the Food and Drug Administration, the National Institutes of Health, and/or the Office for Human Research Protections), or other domestic or foreign government bodies if required by law and/or necessary for oversight purposes.
- ☒ Hospital accrediting agencies.
- ☐ A data and safety monitoring board organized to oversee this research, if applicable.
- ☐ Other, specify: _____

We recognize that some of those who receive protected health information may not have to satisfy the privacy requirements that we do and may redisclose it, so we share your information only if necessary and we use all reasonable efforts to request that those who receive it take steps to protect your privacy.

5. **For how long will protected health information about me be used or shared with others?**
   - There is no scheduled date at which your protected health information that is being used or shared for this research will be destroyed, because research is an ongoing process. Research information may be analyzed and re-analyzed in light of scientific and medical advances, or reviewed for quality assurance, oversight, or other purposes.

6. **Statement of privacy rights:**
   - You have the right to withdraw your permission for the researchers and participating Partners entities to use or share your protected health information. We will not be able to withdraw all of the information that already has been used or shared with others to carry out the research or any information that has been used or shared with others to carry out related activities such as oversight, or that is needed to ensure the quality of the study. If you withdraw your permission, you cannot participate further in the research. If you want to withdraw your permission, you must do so in writing by contacting the researcher listed as the Study Contact.
   - You have the right to choose not to sign this form. If you decide not to sign, you cannot participate in this research study. However, refusing to sign will not affect your present or future care and will not cause any penalty or loss of benefits to which you are otherwise entitled.
   - ☐ You have the right to request access to your protected health information that is used or shared during this research and that relates to your treatment or payment for your treatment, but you may access this information only after the study is completed. To request this information, please contact the researcher listed under Study Contacts on the consent form.

PUBLICATION OF RESULTS OR USE FOR TEACHING PURPOSES

The results of this study may be published in a medical book or journal or used for teaching purposes. However, your name or other identifiers will not be used in any publication or teaching materials without your specific permission.

Research Consent Form

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Subject Identification

REQUEST FOR MORE INFORMATION

You may ask more questions about the study at any time. The investigator(s) will provide their telephone number so that they are available to answer your questions or concerns about the study. You will be informed of any significant new findings discovered during the course of this study that might influence your continued participation. A copy of this consent form will be given to you to keep.

If you want to speak with someone not directly involved in the study about your rights as a research subject, your participation in the study, any concerns you may have about the study, or a research-related injury, contact a representative of the Human Research Committee at (617) 424-4100. You can also contact them if you feel under any pressure to enroll or continue to participate in this study.

REFUSAL OR WITHDRAWAL OF PARTICIPATION

Participation in this study is voluntary. Refusal to participate or dropping out of the study at any time will involve no penalty or loss of benefits to which you are otherwise entitled or affect your present or future care by the doctors or the participating hospitals. In addition, the doctor in charge of this study may decide to end your participation in this study at any time after he/she has explained the reasons for doing so and has helped arrange for your continued care by your own doctor, if needed. Please also see the statement of privacy rights above if you wish to withdraw permission for your health information to be used and shared for study purposes.

INJURY STATEMENT

If you are injured during the course of the study and as a direct result of this study, you should contact the investigator at the number provided under the Study Contacts section in this form. You will be offered the necessary care to treat that injury. This care does not imply any fault or wrong-doing on the part of the Partners institutions participating in this study or the doctor(s) involved. Where applicable, the appropriate Partners institution participating in this study reserves the right to bill third party payers for services you receive for the injury and to make other decisions concerning payment in such instances. The Hospitals will not provide you with any additional compensation for such injuries.

CONSENT TO PARTICIPATE IN RESEARCH AND AUTHORIZATION TO USE OR RELEASE INDIVIDUAL HEALTH INFORMATION FOR RESEARCH

I confirm that the purpose of the research, the study procedures, the possible risks and discomforts and potential benefits that I may experience have been explained to me. Alternatives to my participation in this research study also have been discussed. All my questions have been answered. I have read this consent form. My signature below indicates my willingness to participate in this research study and my authorization to use and share with others my "protected health information" as described in the preceding paragraphs.

Subject Population:	Women above the age of 18 years having Pap tests performed		
IRB Protocol Number:	2003P-001658	Sponsor Protocol Number:	n/a
Consent Form Valid Date:	March 10, 2005	Amendment Number Approved:	1
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Research Consent Form

Brigham and Women's Hospital
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Version 5.1.1 - November 2004

Subject Identification

SIGNATURES:

Subject or Parent(s), if minor child — Date/Time

OR, if applicable, individual authorized by subject to make health care decisions

Court-appointed Guardian/Health Care Proxy — Date/Time

OR

Family Member/Next-of-Kin — Date/Time

Identify relationship to subject:_____

Subject's preferred contact information during course of study:_____

I have explained the purpose of the research, the study procedures, identifying those that are investigational, the possible risks and discomforts and potential benefits. I have answered any questions regarding the research study to the best of my ability.

Investigator/Individual Obtaining Consent — Date/Time

In certain situations, the Human Research Committee will require the use of a subject advocate in the consent process. The subject advocate is an individual who has no vested interest in the research and who agrees to act as an impartial third party in the consent process.

Subject Advocate (if required by the HRC for this study) — Date/Time

Subject Population:	Women above the age of 18 years having Pap tests performed		
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For questions about your rights as a research participant, contact the Partners Institutional Review Board (a group of people who review research to protect your rights) at:

Partners Human Research Committee
116 Huntington Ave., Suite 1002
Boston, MA 02116
617-424-4100

It may be necessary to contact you at a future date regarding new information about your Pap results. For this reason, we ask that you notify the clinic or hospital where you receive your Pap test of any changes in your address.

[redacted]

APPROVED

MAR - 1 2005

HUMAN RESEARCH COMMITTEE

[redacted]
DEPARTMENT OF PATHOLOGY
55 Fruit Street
Boston, MA 02114

U.S. AIR FORCE ACADEMY HOSPITAL
10th MEDICAL GROUP
DEPARTMENT OF PATHOLOGY
4102 Pinion Drive
US Air Force Academy, CO 80840

TRIPLER ARMY MEDICAL CENTER
and the
121st GENERAL HOSPITAL
DEPARTMENT OF PATHOLOGY
Unit #15244 BLD 7005
APO AP 96205-5244

[redacted]
DEPARTMENT OF PATHOLOGY
6900 Georgia Avenue NW
Washington, DC 20307-5001

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

For questions about the study, contact the investigator at:

David C. Wilbur, M.D.

Massachusetts General Hospital

55 Fruit Street

Boston, MA 02114

617-726-7943

INTERNET-BASED CERVICAL CANCER SCREENING RESEARCH PROGRAM

Information for Patients and Providers

APPROVED

MAR - 1 2005

HUMAN RESEARCH COMMITTEE

- ***Research project involving Army, Air Force and civilian investigators associated with 4 major medical hospitals.***
- ***Studies the ability of an automated screening instrument to look at Pap tests and select appropriate images to show to health care providers that interpret Pap tests (cytotechnologists and pathologists).***
- ***Pap tests processed and read in the usual manner plus by an instrument to compare accuracy.***
- ***Involves no change in your health care or follow-up.***
- ***No questionnaire to answer.***
- ***Privacy is protected.***

WHAT IS THE INTERNET-BASED CERVICAL CANCER SCREENING PROGRAM?

This is a clinical trial (a type of research study). Clinical trials only include patients who choose to take part. **Please take time to read this brochure and decide if you wish to participate**. You are being asked to be a part of this study because you are having a Pap test today.

WHY IS THIS STUDY BEING DONE?

The purpose of this study is to find out if Pap tests can be photographed and the images sent by to another laboratory for interpretation. Currently, Pap tests are sent to one laboratory that processes, stains and interprets all of the tests. However, when there are too few specialists available to read the tests, reports may be delayed for weeks or months. If we can send images of the test to other laboratories, those laboratories could help with the workload.

HOW MANY PEOPLE WILL BE IN THE STUDY?

About 5000 women.

If you are not between the ages of 18-65 you may not participate in this study.

WHAT IS INVOLVED IN THE STUDY?

You only have to have your scheduled Pap test taken. Your Pap test will be sent to the usual laboratory for interpretation. After that laboratory is done reporting your Pap test result, your Pap test will be loaded onto an automated machine that will screen the slide for abnormal cells and photograph the most abnormal cells on your slide. These images will be sent to another laboratory to a secure website, along with the clinical information (such as your age, day of your last menstrual period, contraceptive or hormone use, and any history of abnormal Pap tests, bleeding or cancer). The second laboratory will look at the Pap test a second time, without knowing the first result, and send that report by e-mail to a central investigator, who will correlate these results with your actual results to see if they are the same. If they are not the same, and the investigators find an abnormality that was not detected at the first laboratory, that laboratory and your provider will be notified and a third (and possibly a fourth) pathologist will help to determine the correct interpretation.

HOW LONG WILL I BE IN THE STUDY IF I CHOOSE TO PARTICIPATE?

You will be in the study until the second result of your test is recorded. You will be notified of that result only if it is significantly different from your first result. By significantly different, we mean that your care would be different from what you would have with the initial result.

WHAT ARE THE RISKS AND BENEFITS OF THE STUDY?

1. The major risk of the study is that the investigators will find an abnormality that was not initially found on your Pap test. Your doctor will inform you of any significant change in your Pap test.

2. The benefit to you is that your Pap test will be reviewed by at least two different specialists and an instrument designed to detect abnormal cells. If at least two people agree to your Pap interpretation, there is a much lower chance of missing abnormal cells on your test.

WHAT OTHER OPTIONS DO I HAVE?

You may decide not to be in the study. Your Pap test will be processed and reported by the usual route only.

WHAT ABOUT CONFIDENTIALITY?

We make every effort to keep your personal information confidential. Your actual name, date of birth, and social security number will not be used in the study. Only those people who need to have clinical information to make an interpretation on your test will have access to your information. We cannot guarantee absolute confidentiality. Your personal information may be disclosed if required by law. Organizations that may inspect and/or copy your research records for quality assurance or data analysis include groups such as the Institutional Review Board (IRB) of the Partners hospitals.

WHAT ARE MY RIGHTS AS A PARTICIPANT?

You may choose not to take part in this study and may leave the study at any time. Leaving the study will not result in any penalty or loss of benefits to which you are entitled. We will tell you any new information that may affect your health, welfare, or willingness to stay in this study.